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Serum Calcitonin in Small Cell Carcinoma of the Prostate*†

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ABSTRACT

Small cell carcinoma (SCC) of the prostate is a rare and recently recognized subtype of prostate cancer. The neuroendocrine component of the prostate carcinoma is becoming more frequently detected in classic adenocarcinoma of the prostate. Clinically, these tumors represent a considerable portion of so called androgen independent prostatic carcinomas. It has been hypothesized that the neuroendocrine cells being admixed with adenocarcinoma is selected and emerges as a hormone refractory carcinoma after the androgen blockade. The SCC shows a spectrum from a mixed adenocarcinoma with SCC component to the extreme case of pure SCC. Characteristically, prostatic SCC shows low measurable serum level of traditional prostate tumor marker, prostatic specific antigen (PSA). Instead, SCC secretes several neural peptides and calcitonin (CT) is one of them. The usefulness of serum CT as a neuroendocrine marker was evaluated retrospectively in 16 patients with SCC of the prostate (5 pure SCCs and 11 combined adenocarcinoma and SCCs). The serum CT was measured by radioimmunoassay. In all the patients, serum CT level was measured after SCC was diagnosed histologically. All 16 patients presented with advanced tumor with extensive metastasis. Nine (56 percent) out of 16 cases showed elevated serum CT (range 42 ~ 2,654 pg/ml) and chemically supported the diagnosis of SCC. Owing to the retrospective nature of the study, the serum CT was measured only once in most of the cases, and the value of monitoring the disease progress or the responsiveness to the chemotherapy could not be evaluated. Survival analysis by logrank test did not show statistically significant prognostic value of serum CT in SCCs of the prostate. However, patients with extremely high serum CT level tend to have poor survival. Future studies are needed for further evaluation of serum CT as a disease monitor and prognostic marker in SCC of the prostate. Serum CT may have a role as a tumor marker in the early diagnosis of SCC of the prostate, which often is not diagnosed until the advanced stage.

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Introduction

There has been recent recognition of small cell carcinoma (SCC) of the prostate as a rare subtype of prostate cancer. The neuroendocrine differentiation of prostatic carcinomas has been pointed out particularly in relation to its diagnostic, prognostic, and therapeutic implications. The histogenesis of SCC of the prostate is uncertain. Studies suggest that they are a heterogeneous group of tumors arising from multipotential prostatic epithelium.[1,2,3] The majority of SCC of the prostate often combines with adenocarcinoma and many cases apparently arise during the course of progression of classic prostatic carcinoma.[1]

Pure SCC of the prostate is the extreme case of the spectrum and is rare. The SCC of the prostate tumor contains and secretes several neural peptides, either entopic or ectopic. Entopic hormones, particularly serotonin and calcitonin (CT), are more commonly detected than ectopic ones.[3,4] The small cell nature of the carcinoma is determined by histopathological examination. Immunohistochemical stainings, particularly neuron-specific enolase (NSE) and chromogranin A, are used to support the pathological diagnosis of neuroendocrine differentiation.[2,5,6] Both are useful markers for neuroendocrine tumors regardless of the hormonal polypeptide produced. The expression of specific neural peptides in SCCs of the prostate has also been demonstrated immunohistochemically in several studies.[3,5,6,7] No reports are available demonstrating measurement of serum levels of neural peptides as serum markers in patients with SCC of the prostate. The object of this study is to evaluate retrospectively the diagnostic and prognostic value of serum CT in patients with SCC of the prostate.

Materials and Methods

From the 1991 to 1994 files of laboratory tests and surgical pathology of The University of Texas M. D. Anderson Cancer Center, records were retrieved of 16 patients with SCC of the prostate who had serum calcitonin measurements. Histopathological diagnosis was based on the pathology report of M. D. Anderson Cancer Center; clinical information was obtained from a review of medical records. The determination of serum CT was done by a commercial kit based on sequential and competitive radioimmunoassay.*

Calcitonin is captured by 2 days of incubation with anti-calcitonin (goat) at 2 to 8°C. ^{125}I-calcitonin is added sequentially for the competitive binding with another overnight incubation at 2 to 8°C. After adding anti-goat immunoglobulins as a precipitant and short incubation at the supernatant is decanted and the tube with the precipitate is counted for the radioactivity with gamma-counter. The reference range for adult men in our laboratory is ≤26 pg/ml. Serum CT was measured when the initial pathological diagnosis of SCC of the prostate was made, and serum prostate specific antigen (PSA) was also measured at the same time in all cases. The reference range for serum PSA in our laboratory is 0 to 4 ng/ml. Information about disease progress and therapy were obtained from reviewing the chart. Survival was analyzed by logrank test between the normal and abnormal serum CT groups (cutoff point = 26 pg/ml) as well as the low and high serum CT groups (cutoff point = 100 pg/ml).

Results

Among the 16 evaluable cases, 15 patients were white males and one patient was Hispanic. The age of the patients ranged from 49 to 80 years. The pathological diagnosis showed either pure SCC or mixed adenocarcinoma and

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SCC. All the diagnoses were obtained from the tumor biopsy material of either needle biopsies, transurethral resections of the prostate, or biopsies of the metastatic nodule. The total 16 cases were divided into two groups (table I). Group I included 8 cases with prostatic SCC initially diagnosed at the beginning of the patient's presentation. Of this group I, 5 cases were pure SCC, and 3 cases were mixed adenocarcinoma and SCC. Among group I, 6 cases were stage D, and 2 cases were stage B at the initial diagnosis. The 2 stage B cases eventually progressed to stage D with metastatic diseases (table II).

The 8 cases in group II were characterized by initial diagnosis of adenocarcinoma. The emergence of SCC occurred during the course of the disease. For these cases the pathological diagnostic term of transformation to SCC was used. Second or third tissue biopsies were performed in these cases owing to: (1) recurrence of urinary obstructive symptoms with recurred mass; (2) development of metastatic lesion; or (3) minimal response or refractoriness to antiandrogen hormonal therapy. Of the group II 8 cases, 3 showed only SCC, 2 showed mixed carcinoma with predominant SCC component, 2 showed mixed carcinoma with predominant adenocarcinoma component, and 1 revealed mixed adenocarcinoma and carcinoid on subsequent tissue biopsies (table III). Four of the group II patients had stage D diseases, 3 had stage C diseases, and 1 had stage B disease initially. All 8 patients in group II progressed to stage D disease by the time the diagnosis of SCC was made (table III).

The pathological grading of the adenocarcinoma component in both group I and II cases varied from grade II to grade IV (tables II and III). Time interval from initial diagnosis of adenocarcinoma to the emergence of transformed SCC ranged from 5 months to 120 months with a median of 28 months and a mean of 40.6 months (table III).

Characteristically, 7 out of 8 group I patients who initially presented with SCC showed serum PSA levels within the reference range (<0.3 to 2.9 ng/ml), but only 1 patient with mixed adenocarcinoma and SCC had an elevated serum PSA level of 19.8 ng/ml (table II). Seven out of 8 group II patients with initial adenocarcinoma had elevated serum PSA (8.2 to 119 ng/ml) at the beginning of the disease, and the follow-up measurements showed low serum PSA levels (<0.1 to 1.1 ng/ml) in 5 out of these 7 patients by the time the disease progressed to SCC (table III). Two patients who revealed elevated serum PSA, then showed mixed adenocarcinoma and SCC. They had persistent presence of adenocarcinoma component on follow-up (table III).

Elevated serum CT levels were observed in 3 out of 8 patients in Group I and 6 out of 8 patients in Group II. A total of 9 patients out of 16 patients (56 percent) had elevated serum CT levels (table IV). The range of elevation varied widely from 42 pg/ml to 2,654 pg/ml (tables II and III).

All 16 patients developed multiple lymph node, bone, or visceral metastasis

TABLE I

Small Cell Carcinoma of the Prostate (16 Cases)

Histology at Presentation	*Number of Cases*
Small Cell Carcinoma (Group I)	8
Pure small cell carcinoma	5
Mixed adeno and small cell carcinoma	3
Adenocarcinoma[a] (Group II)	8
Transformed to small cell carcinoma	3
Transformed to adeno & small cell carcinoma	5

[a]These eight cases had initial diagnosis of adenocarcinoma and small cell carcinoma emerged during the course of the disease.

(table V). Among the 8 patients with bone metastases, 3 patients who initially presented with SCC (2 pure SCCs and 1 mixed adenocarcinoma and SCC) showed osteolytic bony metastatic lesions.

The therapeutic modalities for the adenocarcinoma were either surgery or radiation treatment plus androgen blockade. Upon the diagnosis of SCC, chemotherapy was added. Six out of 8 group I patients died of disease at 1, 8, 19, 23, 36, and 38 months after diagnosis (table II). The remaining 2 patients are still alive with the disease (table II). In group II, 4 out of 8 patients died of disease at 4, 8, 15, and 19 months after the emergence of the SCC (table III). Two of these patients had only the SCC component on follow-up biopsies, and 2 patients showed mixed SCC and adenocarcinoma with the SCC component predominating (table III). The remaining 4 patients are alive with the disease (table III).

Survival analysis by logrank test showed no statistically significant difference between the normal and elevated

TABLE II

Group I: Small Cell Carcinoma of the Prostate at Presentation (8 Cases)

Age (yr)	*Initial Diagnosis*	*Grade*	*Initial Stage*	*Emerg. of SCC (mo)*	*Metastasis*	*PSA (ng/ml)*	*CT (pg/ml)*	*Treatment*	*Follow–up (Survival in months)*
80	SCC		B	Initital	Liver, adrenal, LN	0.4	17	Chemo, RT	DOD (19)
55	SCC		D	Initial	Liver, LN, brain	0.3	16	Chemo, RT	DOD (8)
78	SCC		D	Initial	Bone, liver	2.6	186	RT, chemo, horm	DOD (1)
58	SCC		D	Initial	Bone, LN, liver	1.2	745	Chemo	AWD (19+)
76	SCC		D	Initial	Lung, LN	2.9	20	Chemo	AWD (6+)
66	ADE + SCC[a]	IV	D	Initial	Bone	2.2	8	Chemo, horm	DOD (23)
63	ADE + SCC[a]	III	D	Initial	LN, liver, lung, peri–neum, bone, adrenal	<0.3	42	Horm, chemo RT	DOD (38)
79	SCC + ADE[b]	IV	B	Initial	Liver, LN	19.8	12	TURP, chemo, horm	DOD (36)

[a]Histology showed predominantly adenocarcinoma but with small cell carcinoma.
[b]Histology showed predominantly small cell carcinoma but with adenocarcinoma.
SCC = small cell carcinoma.
ADE = adenocarcinoma.
LN = lymph node
PSA = prostate specific antigen.
CT = calcitonin.
Chemo = chemotherapy.
RT = radiation therapy.
Horm = hormone therapy.
TURP = transurethral resection of the prostate.
DOD = died of disease.
AWD = alive with disease.

TABLE III

Group: II Transformed Small Cell Carcinoma of the Prostate from Initial Adenocarcinoma (8 Cases)

Age (yr)	Initial Diagnosis	Grade	Initial Stage	Emerg. of SCC (mo)	Metastasis	PSA[a] (ng/ml)	CT (pg/ml)	Treatment	Follow–up (Survival in months)
68	ADE	III	D	ADE+ Carcin(8)	Lung, adrenal	8.2/ 1.1	88	Horm, chemo TURP, RT	AWD (8+)
64	ADE	II	D	ADE+ SCC(18)	Liver, LN, bone, lung, skin	17.9/ 13.5	715	Horm, TURP, RT, chemo	AWD (15+)
49	ADE	III	C	ADE+ SCC(48)	LN, lung	28/33	<10	Horm, orch, TURP, RT, chemo	AWD (8+)
58	ADE	III	D	SCC+ ADE(11)	LN, Bone	119/ 1.1	265 4	Horm, TURP, RT, chemo	DOD (19)
62	ADE	II	D	SCC+ ADE(77)	LN, Bone, liver	2.6/ 1.0	194 0	Orch, TURP	DOD (4)
53	ADE	IV	B	SCC(5)	LN, liver, Bone Brain	9.7/ 0.5	10	Horm, chemo, RT	DOD (8)
63	ADE	III	C	SCC(38)	Perineum	21.3/ <0.1	48	Chemo, RT, orch, horm, cryo	AWD (17+)
61	ADE	II	C	SCC (120)	Liver, perineum, Brain	8.2/ 0.2	223	RT, Horm, chemo, cryo, TURP	DOD (15)

[a]The first prostate specific antigen value was taken at initial diagnosis. The second prostate specific antigen value was taken at the occurrence of small cell carcinoma.

ADE = adenocarcinoma.
Carcin = carcinoid.
SCC = small cell carcinoma
LN = lymph node.
PSA = prostate specific antigen.
CT = calcitonin.
Chemo = chemotherapy.
RT = radiation therapy.
Horm = hormone therapy.
TURP = transurethral resection of the prostate.
Orch = orchiectomy.
Cryo = cryosurgery.
DOD = died of disease.
AWD = alive with disease.

serum CT groups (P = 0.64; figure 1A). If a cutoff point of 100 pg/ml is chosen to define the low and high serum CT group, the survival curve of the low serum CT group is completely above the high serum CT group (figure 1B). However, the difference is not statistically significant (P = 0.19).

TABLE IV

Serum Markers of Small Cell Carcinoma of the Prostate (16 Cases)

Ssem Markers	Group I Elevated (%)	Group I Normal (%)	Group II Elevated (%)	Group II Normal (%)	Total Elevated (%)	Total Normal (%)
PSA at initial diagnosis of adenocarcinoma only			7 (88)	1 (12)	7 (88)	1 (12)
PSA at initial diagnosis of SCC or after transformed to SCC	1 (12)	7 (88)	2 (25)	6 (75)	3 (19)	13 (81)
Calcitonin	3 (38)	5 (62)	6 (75)	2 (25)	9 (56)	7 (44)

Discussion

Prostatic carcinoma is the most commonly diagnosed malignancy in men in the U.S. and the second most common cause of cancer-related deaths in men in the U.S.[4,8] The natural history of prostatic cancer is variable, and there is a wide range of clinical behavior from indolent to rapidly progressive tumors. So far it has not been reliably possible to distinguish prostatic cancers of different behavior with their different therapeutic responsiveness.[5,8,9] The most valuable prognostic indicators in current use are probably tumor stage and grade. Recent recognition of SCC of the prostate as a rare subtype of the prostatic cancer[10] has drawn attention to the prevalence of neural elements and possible effects of neuropeptides on the behavior or progression of the disease.

Small cell carcinoma of the prostate is a highly aggressive tumor, and patients frequently present with advanced disease. The tumor characteristically manifests with a large primary mass with a high frequency of visceral metastasis compared to the relative low bony metastasis.[2,12] Typically, the majority of the patients do not have elevated serum PSA, and the tumor is considered unresponsive to androgen ablation.[8,12] When these features are present in a patient with prostatic carcinoma, the clinician should suspect the presence of SCC.

Our data confirm these reports by showing that at the diagnosis of SCC, the levels of PSA were elevated in only 3 out of 16 (19 percent) cases. All 3 cases with high PSA had the adenocarcinoma components. Ten of 16 our patients died of disease and confirmed that SCC of the prostate is an aggressive tumor. Although there is a prevalence of classic prostatic carcinoma in black males, it is noteworthy that 15 out of 16 cases were white

TABLE V

Metastasis of Small Cell Carcinoma of the Prostate (16 Cases)

Metastatic Site	Number of Cases Group I	Group II	Total
Lymph node	6	5	11
Liver	6	4	10
Bone	4	4	8
Lung	2	3	5
Adrenal gland	2	1	3
Perineum	1	2	3
Brain	1	2	3
Skin	0	1	1
Total	22	22	44

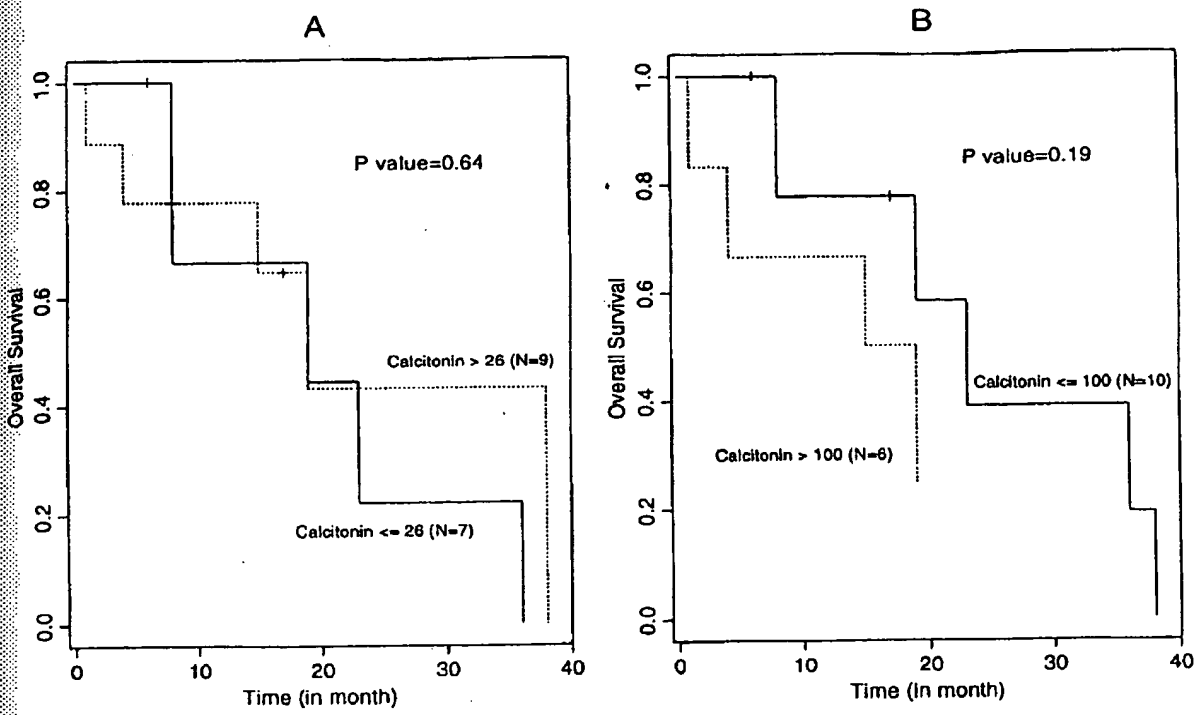

FIGURE 1A. Survival analysis by logrank test showed no statistically significant difference between the normal (< = 26 pg/ml) and elevated (>26 pg/ml) serum calcitonin groups (P = 0.64).

FIGURE 1B. The survival curve of the low calcitonin group (< = 100 pg/ml) is completely above the high calcitonin group (>100 pg/ml) when the cutoff point of 100 pg/ml is chosen. However, the difference is not statistically significant (P = 0.19).

males and the remaining 1 was a Hispanic male.

The presence of neuroendocrine cells in the normal prostatic ducts and acini are well recognized.[11] As methods of detection have become more sophisticated, the number of prostatic adenocarcinoma with focal neuroendocrine differentiation reported has steadily increased to 47 percent[3] and even to 100 percent.[12] The major contributing factor for the sensitive detection was the advent of immunohistochemistry with a variety of neuroendocrine markers and specific antibodies to neural peptides. These special staining methods could highlight the cells of neuroendocrine differentiation among conventional adenocarcinoma looking histology. However, the significance of these neuroendocrine-cells present in prostatic carcinoma are still unknown.

A few studies[14,15] suggest possible involvement of neuroendocrine factors in the progression of prostatic carcinoma by either developing their own neoplastic process (SCC of the prostate) or causing paracrine progression of the tumor. Cohen et al.[10] suggested that the presence of neuroendocrine cells be considered an independent prognostic variable.

Serum CT was chosen for the evaluation not only because CT is a more frequently detected hormone compared to the other neural peptides in the tissue of SCC of the prostate,[3,4] but also because the serum CT detection method is more readily available in our laboratory. Serum CT is a well-known useful marker for the diagnosis and monitoring of medullary carcinoma of the thyroid gland.[16] Although CT is recognized as one of the most commonly detected hormones in the tissue of SCC of the prostate, there

has been no previous study done to evaluate the serum CT levels in these patients.

One article[7] specifically reported two cases of calcitonin-secreting carcinomas of the prostate proved by immunohistochemical and ultrastructural analysis. Our study confirms the neuroendocrine nature of the carcinoma by elevated serum CT level in 56 percent of the cases. The result showed possible implication of serum CT as an adjuvant diagnostic serum marker in SCC of the prostate which characteristically would not express elevated serum PSA. Our initial serum CT study for SCC of the prostate showed a wide range of serum concentrations and elevations, but it but did not have the prognostic value. Even though statistically not significant, our preliminary data suggested that an extremely high serum CT may be a poor prognostic factor.

Serum CT may be a good candidate for a disease monitoring serum marker in SCC of the prostate. Its value should be evaluated with more cases and follow-up in the future. All 16 cases of this study demonstrated obvious SCC features histologically. Future evaluation of neuroendocrine serum markers in the adenocarcinoma of the prostate as a possible prognostic parameter is suggested since more and more neuroendocrine components are recognized or supposedly evolve during the androgen blockade therapy among the conventional adenocarcinoma of the prostate.

In summary, it is important to be aware of the existence of SCC of the prostate. There appears to be increasing emergene of SCCs of the prostate as hormone refractory carcinomas after androgen blockade therapy. Serum CT can be used as an adjuvant diagnostic test for suspected cases of SCC of the prostate and may have a role as a tumor marker in the early diagnosis of the disease. This retrospective evaluation does not demonstrate the prognostic value of the serum CT in SCC of the prostate. Future studies are needed for further evaluation of serum CT as a disease monitor and prognostic marker in SCC of the prostate.

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